Genetics inMedicine | CORRESPONDENCE

Response to "The use of ACMG secondary findings recommendations for general population screening: a policy statement of the American College of Medical Genetics and Genomics (ACMG)"

In their Statement "Opportunistic secondary genetic testing in the course of whole exome/genome analysis and the same analysis in unaffected individuals seeking to know their risks for disease: A distinction without a difference." the ACMG Board of Directors is proposing a flawed and illogical policy.[1] The statement draws a distinction between offering testing for the ACMG 56™ or ACMG 59™ as secondary findings in families undergoing exome or genome analysis, which the Board supports,[2] and offering the same tests in unaffected individuals seeking to know their genetic risks, which the Board apparently does not. Although patients undergoing exome or genome analysis generally have a disease phenotype, their parents usually do not, and, in any case, most patients and nearly all parents are undergoing exome or genome analysis for phenotypes that do not result from pathogenic variants in the genes on the ACMG 56™ or ACMG 59™ list. Therefore, offering analysis of these genes as an option to unaffected individuals seeking genetic risk information is no different than offering patients and their parents the option to have them analyzed as secondary findings during the course of clinical exome or genome analysis.

The policy statement also seeks to justify a distinction between secondary findings as part of exome or genome analysis and primary analysis of these same genes in individuals seeking to know their genetic risks on the basis of the ACMG SF v2.0 list of genes because the latter have not been validated for general population screening. This statement is misleading because it suggests such testing has been better validated in patients and parents undergoing exome or genome analysis than in unaffected individuals seeking to know their genetic risks. It has not.

A subsequent clarification[3] posted online on 30 April 2019 unfortunately reaffirms and perpetuates the inconsistency. In paragraph 6, they state "ACMG does not sanction the use of this 'package' of genes for population-based screening until penetrance is better understood in asymptomatic individuals and appropriate follow-up care approaches can be assured" but then point out in paragraph 8 that "[w]e also understand that the issue of penetrance is equally relevant to the follow-up of patients who are identified to have variants in the ACMG list through opportunistic analysis of variants in the ACMG gene list, during sequencing for other indications." A need for appropriate follow-up care approaches does not distinguish between the two groups. In short, without justification, the ACMG is endorsing screening these genes for one group of individuals unaffected with disorders associated with this set of genes but not another group of individuals unaffected with disorders associated with this set of genes.

We concur with the ACMG in calling for outcomes research to establish the efficacy of interventions in asymptomatic patients with pathogenic and likely pathogenic variants in known associated genes. Invitae has already performed analysis of a larger set of genes chosen in the spirit of the ACMG SF v2.0 in >4000 individuals who chose to undergo testing to identify their genetic risks. We show ~16% of individuals have unsuspected but actionable findings and presented these results at the annual ACMG and American Society of Human Genetics (ASHG) meetings over the past year. The ACMG Board of Directors statements constitute a strategic misstep that will inevitably render the ACMG irrelevant in the larger discussion on this important and evolving development in genomics. In contrast, the Centers for Disease Control and Prevention's Office of Public Health Genomics should be congratulated for issuing a far more thoughtful discussion of the benefits of genetic testing for unaffected individuals in the population for "tier I" tests (hereditary breast cancer, Lynch syndrome, and familial hypercholesterolemia).[4]

DISCLOSURE

All authors are employees and stock holders in Invitae, a commercial genetic testing company that has pioneered the use of genetic testing of unaffected individuals seeking to know their risk for serious, unsuspected yet actionable oncological and cardiovascular disorders. In addition, RLN is a consultant for Pfizer Pharmaceuticals, and a consultant and stock holder in Maze Therapeutics and Genome Medical.

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